

### REMARKS

Claims 1-7 are pending and have been amended. Claims 8 and 9 have been added. Claims 1-9 are therefore pending in the application.

Applicants have amended claims 1-3 so as to remove non-elected subject matter. Applicants have amended claim 4 to include the phrase "a pharmaceutically acceptable carrier" in claim 4 and to delete the diseases recited in the preamble of this claim. Support for these amendments can be found throughout the specification, e.g., at page 15, lines 23-27. Applicants have amended claims 5-7 to clarify further the nature of the reactant used to introduce the substituent R<sup>1</sup> in step (a) of the claimed processes. Support for this amendment can be found throughout the specification, e.g., at page 3, line 26 through page 4, line 16. Support for new claims 8 and 9 can be found throughout the specification, e.g., page 14, line 24 through page 15, line 22 and page 16 line 4-11. Finally, Applicants have amended the specification to include a specific reference to earlier filed applications as required by the Examiner. The foregoing amendments introduce no new matter.

Reconsideration of the application, as amended, is respectfully requested in view of the remarks below.

### Claim Objections

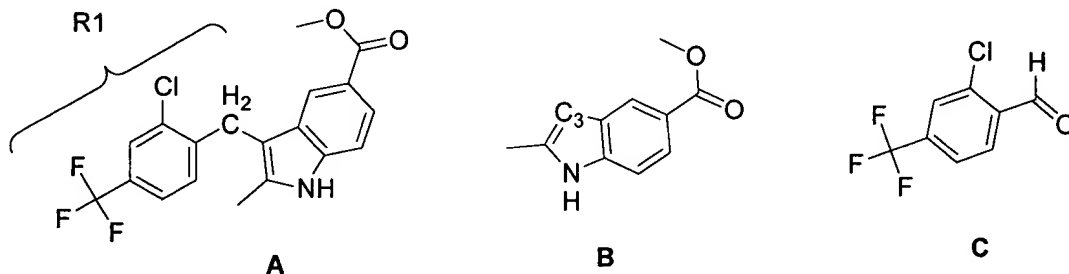
Claims 1-7 are objected to because of informalities (Action, page 6, lines 8-21).

According to the Action, "claim 4 does not indicate that a carrier is present with the composition." (Action, page 6, line 9). This objection is moot in view of the amendment of claim 4.

According to the Action, "[c]laim 5-7 refer to an 'aldehyde corresponding to R<sup>1</sup>' in step (a). The phrase "aldehyde corresponding to R<sup>1</sup>" is unclear." (Action, page 6, lines 13-14).

Applicants disagree. Step (a) in claims 5-7 covers the conversion of compounds having formula (2) to compounds having formula (3), i.e., the coupling of the R<sup>1</sup> moiety to C-3 of the indole ring in formula (2). According to the specification, "[c]ompound (2) can be converted into compound (3) by reacting it with silanes represented by triethylsilane and aldehydes corresponding to R<sup>1</sup>" (specification, page 4, lines 10-11 and 14-16). By way of example,

Applicants refer to the synthesis of the compound “3-(2-chloro-4-(trifluoromethyl)benzyl)-5-(methoxycarbonyl)-2-methyl indole” (compound **A** below, described in Production Example 7 at page 22 of the specification). Compound **A** corresponds to a compound having formula (3) in which  $R^1$  is a 2-chloro-4-(trifluoromethyl)benzyl group. Compound **A** is prepared from 5-(methoxycarbonyl)-2-methylindole (compound **B** below) and 2-chloro-4-(trifluoromethyl)benzaldehyde (compound **C** below). It is compound **C** that ultimately becomes  $R^1$  in compound **A**. The aldehyde group (i.e.,  $-C(O)H$ ) in **C** becomes a  $-CH_2$  group in **A** during this process.



One of skill in the art reading Applicants' specification would understand the phrase “aldehyde corresponding to  $R^1$ ” in claim 5-7 to mean a compound having the same carbon content and connectivity as  $R^1$ , but with an aldehyde group at the position corresponding to the point of attachment of  $R^1$  to the indole ring. Applicants submit the phrase is sufficiently clear when read in light of Applicants' disclosure and respectfully request withdrawal of the objection.

The Examiner objects to claims 1-7 for containing non-elected subject matter (Action, page 6, line 19). This objection is moot in view of the amendments to claims 5-7.

#### Rejection under 35 U.S.C. § 112, first paragraph

Claim 4 is rejected as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention (Action, page 2, line 20 through

page 3, line 2). To support the rejection, the Office relies on relevant factors set forth in *In re Wands* 8 USPQ2d 1400 (CAFC, 1988) (Action, page 3, lines 3-13). According to the Action:

[I]n order to overcome the rejection, it is suggested that Applicant delete 'preventing' from claim 4, limit claim 4 to the treatment of diabetes and delete all other diseases listed in claim 4 (Action, page 6, lines 4-6).

Claim 4 as amended is directed to a pharmaceutical composition comprising "an indole derivative or a salt thereof according to any one of claims 1-3 and a pharmaceutically acceptable carrier." Applicants' specification provides teachings as to how to make and use the claimed compositions (see, e.g., at page 12, lines 1-16; page 15, line 23 through page 16, line 11 and page 17, line 6 through page 51, line 8). Applicants therefore submit that the compositions covered by claim 4 are enabled by the specification.

Applicants note that the preamble of claim 4 as originally filed included a statement of intended use of the claimed compositions (see underlined passage):

A pharmaceutical composition for preventing and treating impaired glucose tolerance, diabetes, diabetic complications, syndrome of insulin resistance, polycystic ovary syndrome, hyperlipidemia, atherosclerosis, cardiovascular disorders, hyperglycemia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy, tubulointerstitial disorders, renal failure, angiostenosis, distal angiopathy, cerebral apoplexy, chronic reversible obstructions, autoimmune diseases, allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility disorders, impotence, nephritis, cachexia, pancreatitis, or restenosis after PTCA, which comprises,...

Although claim 4 is directed to a pharmaceutical composition, the Office has based the foregoing rejection solely on the breadth of the intended use of the claimed compositions, thereby treating the subject matter of the intended use as a further limitation of the claim. This interpretation is evidenced by the Office's suggestion to delete the gerund "preventing" and "limit claim 4 to the treatment of diabetes and delete all other diseases" in order to "overcome the rejection" (Action, page 6, lines 4-6). Applicants disagree with this interpretation and point out the holding in *Rowe v. Dror*:

...where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation (*Rowe v. Dror*, 112 F.3d 473, 478, USPQ2d 1550, 1553 (Fed. Cir. 1997), emphasis added).

To expedite prosecution, Applicants have deleted the intended use phrase “for preventing or treating...or retinosis after PTCA” in claim 4. However, the foregoing amendment is not to be construed as acquiescence on the part of Applicants to the grounds for rejection. Applicants respectfully request that the rejection of claim 4 be withdrawn for the reasons set forth above.

Applicants have introduced new method of use claims 8 and 9. Specifically, claim 8 is directed to methods of preventing or treating diseases including (but not limited to) diabetes by administering the claimed indole compounds. This claim therefore covers, in part, the cancelled intended use subject matter of claim 4 discussed above. Claim 9 is directed to a method of lowering blood sugar by administering the claimed indole compounds. Applicants therefore wish to address the Office's assertion that undue experimentation would be required to treat or prevent diseases other than diabetes using the claimed indole compounds.

Applicants' invention is based, in part, on the discovery that indole derivatives of formula (I) have, e.g., blood sugar level depressing activity. As such, the claimed compounds can be useful for the treatment of impaired glucose tolerance, diabetes, diabetic complications, syndrome of insulin resistance, polycystic ovary syndrome, hyperlipidemia, atherosclerosis, cardiovascular disorders, hyperglycemia, and hypertension.

According to the Action:

The prior arts do not indicate that the instant compound is useful in ‘preventing and treating’ impaired glucose tolerance, diabetes, diabetic complications, etc. The specification does not cite any patents, journal articles, or other literature to support that the instant indole derivative prevents and treats all of the diseases claimed in claim 4. ... The attached articles support that lowering plasma glucose is useful in the treatment of diabetes (Action, page 3, line 20 through page 4, line 1 and page 5, line 21-22).

Applicants acknowledge that the Examiner has determined that the claimed subject matter meets the statutory requirements of novelty and nonobviousness and is enabled for diabetes.

With regard to the use of the claimed compounds to treat diseases other than diabetes, Applicants point out the following articles. Uusitupa et al, *Diabetologia* **1993**, *36*, 1174 and Gall et al., *Diabetologia* **1991**, *34*, 655 that demonstrate that patients having elevated glucose levels, e.g., diabetic patients, are likely to develop cardiovascular disease (due to increase of serum triglyceride levels) and arterial hypertension, respectively. The enclosed article by Cornicelli, *Atherosclerosis* **1997**, *2*, 43, describes the relationship of Troglitazone (a blood sugar lowering compound) with glucose tolerance and the improvement of insulin resistance. Troglitazone is also useful in the prevention of hypertension and hypertriglyceridemia, which are both likely conditions to develop in patients having elevated blood glucose levels (*vide supra* in Gall and Uusitupa). Thus, these references indicate that the level of skill and predictability in the art is such that a blood sugar lowering compound can be expected to have therapeutic utility for both diabetes and diseases related to this condition as is asserted in Applicants' specification.

Applicants submit that some experimentation may be required to practice the invention, but not undue experimentation. It is held in *In re Colianni* and *In re Wands*:

[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance (In *In re Colianni*, 195 USPQ, 150, 153, (CCPA, 1977)).

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine (*In Re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988))

The instant specification provides ample guidance and direction in the form of a roadmap of preferred compound attributes, exemplary compounds, and synthesis procedures along with an art-recognized test method for evaluating plasma glucose and triglyceride levels. Further, the instant specification provides a regimen and recommended dosages for administering the compounds to patients. Thus, a skilled artisan could make and use the claimed invention without undue experimentation.

Thus claim 8 and 9 meet the statutory requirements of 35 U.S.C. 112, first paragraph for the reasons set forth above.

Applicant : Noritsugu Yamasaki et al.  
Serial No. : 09/647,772  
Filed : October 4, 2000  
Page : 16 of 16

Attorney's Docket No.: 14878-065001 / D1-002PCT-  
US

CONCLUSION

Applicant submits that all claims are in condition for allowance

Enclosed is a \$110 check for the One-Month Petition for Extension of Time fee. Please apply any other charges to deposit account 06-1050, referencing Attorney Docket No. 14878-065001.

Respectfully submitted,

*John T. Kendall*  
Reg. No. 50,680

Date: January 26, 2004

*FOR* Robert C. Nabinger  
Reg. No. 33,431

Fish & Richardson P.C.  
225 Franklin Street  
Boston, MA 02110-2804  
Telephone: (617) 542-5070  
Facsimile: (617) 542-8906